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THE RELATION OF RISK FACTORS TO THE DEVELOPMENT OF ATHEROSCLEROSIS IN SAPHENOUS-VEIN BYPASS GRAFTS AND THE PROGRESSION OF DISEASE IN THE NATIVE CIRCULATION

A Study 10 Years after Aortocoronary Bypass Surgery

LUCIEN CAMPEAU, M.D., MARC ENJALBERT, M.D., JACQUES LESPÉRANCE, M.D., MARTIAL G. BOURASSA, M.D., PETER KWITEROVICH, JR., M.D., SHOLOM WACHOLDER, PH.D., AND ALLAN SNIDERMAN, M.D.

Abstract We examined 82 patients 10 years after saphenous-vein aortocoronary bypass surgery to determine their angiographic status and to relate those findings to the risk factors for coronary-artery disease. Of 132 grafts shown to be patent 1 year after surgery, only 50 were unaffected at 10 years. The remainder were narrowed (43) or occluded (39). Disease progression in coronary arteries without grafts was also frequent, both in vessels that were normal (15 of 32) and in those with minor stenosis (25 of 53).

New lesions did not develop in 15 patients, whereas they did in 67 — in the grafts, the native vessels, or both. There was no significant difference between the two groups in the incidence of hypertension, diabetes, or smoking, whereas plasma levels of very-low-density lipoproteins (VLDLs) and low-density lipoproteins (LDLs) were higher, and high-density lipoprotein (HDL) levels were lower in those with new disease than in those without. Univariate analysis showed that plasma cholesterol and triglyceride levels were significantly higher at the time of surgery and at the 10-year examination in those with new lesions. Multivariate analysis indicated that among the lipoprotein indexes, levels of HDL cholesterol and plasma LDL apoprotein B best distinguished the two groups.

The findings indicate that atherosclerosis in these patients was a progressive disease, frequently affecting both the grafts and the native vessels, and that the course of such disease may be related to the plasma lipoprotein levels. (N Engl J Med 1984; 311:1329-32.)

OVER the past 10 years, aortocoronary bypass surgery has become widely accepted.[1] The risks of surgery, the temporary disability after operation, and the very considerable expense — all seem to be offset by the often dramatic clinical improvement and by the evidence in certain categories of disease of decreased mortality after surgery, at least during the first five years. The longer-term outcome is not as well known and will be determined, to an important degree, by the rate at which atherosclerosis progresses in the native circulation or appears within the grafts. With regard to the latter, graft-patency rates appear to be high, and atherosclerosis within them a relatively minor problem over the first five years after surgery.[2] Beyond that period, little is known. We have followed a group of patients for 10 years after aortocoronary bypass surgery. All have undergone sequential coronary angiographic examinations. The present study attempts to relate the development of atherosclerosis in the grafts and the progression of disease in the coronary arteries without grafts to the major risk factors for atherosclerosis.

From the Montreal Heart Institute, University of Montreal, the Department of Epidemiology and Health, and the Cardiovascular Research Unit, Royal Victoria Hospital, McGill University; Montreal, Quebec. Address reprint requests to Dr. Campeau, Montreal Heart Institute, 5000 East, Belanger St., Montreal, PQ H1T 1C8, Canada.

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METHODS

Patient Selection

All the patients had undergone aortocoronary saphenous-vein bypass surgery at the Montreal Heart Institute between September 1969 and August 1972. All had been evaluated angiographically both at two weeks and between 6 and 18 months (one-year examination) after surgery.[3] To be eligible for this study, a patient had to have at least one patent graft at the one-year examination, to have survived for 10 years after surgery, and to have had no reoperation in the interim.

One hundred forty-eight patients constituted the total population that could have been studied; of these, 82 (55.4 per cent) were restudied, and 66 (44.6 per cent) were not. Reexamination was not carried out in the latter group because of age (nine patients were older than 75); illness (eight had congestive heart failure, eight cerebrovascular accidents, five cancer, and two other diseases); refusal to participate by either the patient or the physician (25); or, finally, living too far from the Montreal Heart Institute (nine).

Thus, the study group consisted of 68 men and 14 women, with a mean (±S.D.) age of 58±16 at the time of the reexamination. Those who were restudied were similar to those who were not with respect to their age at the time of surgery (48±15 as compared with 51±17 years), graft-patency rate at one year (90 as compared with 91 per cent), and the presence of angina 10 years after surgery (46 as

Table 1. Grading of Effort Angina before and after Surgery.*

Effort Angina	Before Surgery	After 1 Year	After 10 Years
		number (per cent)	
None	0	59 (72)	30 (37)
Grade 1	1 (1)	9 (11)	0
Grade 2	19 (23)	13 (16)	27 (33)
Grade 3	59 (72)	1 (1)	19 (23)
Grade 4	3 (4)	0	6 (7)

*According to the classification system of the Canadian Cardiovascular Association.

compared with 41 per cent). The clinical status before surgery and 1 year and 10 years after surgery is shown in Table 1. Effort angina was graded according to the classification of the Canadian Cardiovascular Association.[4]

Patients were told to stop smoking and to adhere to a diet low in saturated fats. Since most of them had been referred to us and were examined by us only at intervals of one to two years, no systematic lipid-lowering drug therapy was attempted. Neither anticoagulants nor platelet-active drugs had been systematically prescribed beyond the first six months after surgery. The patients had not taken lipid-lowering drugs for at least three months before determination of their lipid and plasma low-density lipoprotein (LDL) apoprotein B levels.

Angiographic Evaluation

Changes other than total obstruction that developed in the saphenous-vein bypass graft after the one-year examination were designated atherosclerotic.[5] The progression of coronary disease in the native circulation was assessed only in the 85 vessels without grafts. Eleven patients in whom all three coronary arteries had received grafts were therefore excluded from this aspect of the analysis. Progression in the native vessels was defined as (1) the appearance of a stenosis reducing the vessel diameter by at least 50 per cent, (2) further narrowing by at least 20 per cent, or (3) progression of any lesion to the point of total occlusion. The site of greatest narrowing in the graft or native coronary artery was measured by a vernier caliper and expressed as a percentage of the maximal vessel lumen.

Risk Factors

At the time of the 10-year angiographic study, the major risk factors for coronary disease were examined in each patient. Blood pressure, blood sugar level while fasting, cigarette smoking, and plasma lipids were all assessed. Plasma triglycerides and total cholesterol while fasting were measured enzymatically[6,7]; high-density-lipoprotein (HDL) cholesterol was quantified by dextran sulfate–magnesium precipitation,[8] and LDL cholesterol was measured by the following formula: total cholesterol minus (HDL cholesterol + triglycerides) when the plasma triglyceride level was less than 400 mg per deciliter.[9] Plasma LDL apoprotein B was measured by radial immunodiffusion.[10] Plasma cholesterol and triglycerides[11] had also been measured in 70 of the 82 patients just before surgery.

All biochemical measurements were carried out without knowledge of the angiographic findings.

The following definitions are employed in this study: hypertriglyceridemia, a fasting plasma triglyceride level of 200 mg per deciliter or higher; Type IIA hyperlipoproteinemia, an LDL cholesterol level of 200 mg per deciliter or higher with normal fasting triglycerides; Type IIB hyperlipoproteinemia, an LDL cholesterol level of 200 mg per deciliter or higher with fasting hypertriglyceridemia; and hyperapobetalipoproteinemia, an LDL cholesterol level of 200 mg per deciliter or lower with a plasma LDL apoprotein B level of 115 mg per deciliter or higher.[12]

Differences in means between groups were tested by t-tests. Serial multiple logistic-regression fits of the data were obtained to determine which of the above measurements were associated with the appearance of disease when the effects of the others were controlled for.[13]

Results

Frequency of Lesions in Grafts or Progression in the Native Circulation

Of 132 grafts that were patent at 1 year, 93 (70.5 per cent) were still patent at the 10-year examination. Only 50 (37.5 per cent) were unchanged, however, whereas 43 (33 per cent) had atherosclerotic lesions. Although lumen reduction was slight in some instances, 30 of these 43 grafts (70 per cent) had lesions that reduced the lumen by at least 50 per cent, the average decrease being 62±15 per cent. Thirty-nine of the 132 grafts (29.5 per cent) were found to be completely occluded at the 10-year examination. Overall, only 26 patients (31 per cent) had no change in their grafts between the 1-year and 10-year examinations, whereas 39 (48 per cent) had recognizable narrowing in at least one graft, and 17 (21 per cent) had total occlusion of at least one graft.

Among the 85 arteries without grafts, increased narrowing was observed in 25 of the 53 (47 per cent) coronary arteries with preexisting stenoses of more than 20 per cent, whereas new obstruction was noted in 15 of 32 (47 per cent) arteries that had previously been normal.

Risk Factors Related to Changes in Grafts and Native Vessels

The major risk factors for coronary-artery disease were examined in two groups of patients. Group I consisted of 15 patients in whom recognizable atherosclerotic lesions did not develop in unbypassed arteries or in the saphenous-vein bypass grafts in the period between the 1-year and 10-year examinations; Group II consisted of 67 patients in whom new lesions did develop within the same interval, in the bypass grafts, in the native circulation, or both.

The data listed in Table 2 make it evident that little difference existed between the two groups 10 years after surgery in terms of age, prevalence of hypertension, or the number who never smoked, who were ex-smokers, or who continued to smoke. However, as Table 3 shows, the levels of serum lipoproteins 10 years after surgery were shown by univariate analysis to differ significantly between the two groups, with levels of very-low-density lipoproteins (VLDLs) and LDL higher and HDL levels lower in the Group II patients.

In 70 patients, total cholesterol and triglycerides while fasting were measured before surgery. Thirteen of these belonged to Group I, and 57 to Group II. Both the cholesterol and triglyceride levels were significantly higher in Group II than in Group I (cholesterol, 260±47 as compared with 229±42, $P<0.05$; triglycerides, 220±99 as compared with 147±65, $P<0.01$).

Since LDL is a metabolic product of VLDL and since two components of LDL were measured, the

Table 2. Prevalence of Coronary Risk Factors 10 Years after Surgery.

Risk Factor	Group I	Group II
No. of patients	*15*	*67*
Age (mean±S.D.)	58±8	60±8
Sex (M/F)	11/4	58/9
Hypertension (%)	13	12
Diabetes (%)	7	3
Never smoked (%)	27	30
Stopped smoking (%)	33	33
Still smoking (%)	40	37

data were analyzed by multiple logistic regression to identify which variables were most likely to be independent risk factors and which were most likely to differ between groups only because of correlation with other values. First, a complete model was established that included all the variables so that the two groups could be best separated; then each variable in turn was deleted, and the effect of the separation determined. The exclusion of either LDL apoprotein B or HDL cholesterol from the complete model produced significant worsening of the fit (chi-square = 21.95 and 6.68, respectively, both with 1 degree of freedom). A model that included only LDL apoprotein B and HDL cholesterol did almost as well as one with all the measured lipid variables ($P>0.25$), indicating that none of the excluded variables — total cholesterol, plasma triglyceride (whether measured prospectively or retrospectively), or LDL cholesterol — improved the fit significantly. Estimates from the model that included only LDL apoprotein B and HDL cholesterol indicate that for each additional standard deviation of LDL apoprotein B, the odds of being in the diseased group increased by a factor of 13.1. On the other hand, for each reduction of 1 S.D. of HDL cholesterol, the odds of being in the diseased group increased by a factor of 10.2. The inclusion of age, smoking, and sex as covariates did not substantially alter these results.

The frequency of abnormal lipoprotein phenotypes is shown in Table 4. Seventy-nine per cent of the patients in Group I — that is, those without new lesions — had normal lipid levels and normal plasma levels of LDL apoprotein B. One had Type IV hyperlipoproteinemia but normal LDL apoprotein B levels, and one each had Type IIA hyperlipoproteinemia and hyperapobetalipoproteinemia. By contrast, 92 per cent of the patients in Group II had abnormal lipoprotein phenotypes. Just over 50 per cent had hyperapobetalipoproteinemia with or without hypertriglyceridemia, and 39 per cent had Type II hyperlipoproteinemia.

Discussion

In this group of patients, followed for 10 years after saphenous-vein aortocoronary bypass surgery, serial coronary angiographic studies have demonstrated that atherosclerosis in grafts and the progression of coronary disease in the vessels without grafts are both very common. Of the grafts that were patent at 1 year, about one in three were occluded after 10 years, and an additional one in three were narrowed; in addition, new lesions developed or old ones progressed in just under half the vessels without grafts. Thus, after an initial latent period, atherosclerosis emerged as a major factor in our patients, potentially limiting the success of their surgery.[14]

The development of graft atherosclerosis and the progression of disease in the native coronary arteries seemed linked to the levels of plasma lipoproteins, especially those of LDLs and HDLs. A contribution of other factors, such as hypertension, cigarette smoking, and diabetes, to the risk of disease was not detectable in this study, but this is not surprising given the relatively small number of patients studied and the fact that these factors were treated as discrete, not continuous, variables.

The design of this study also limits the extent to which its findings can be generalized. Only a portion of the original group underwent angiography at 10 years, and whereas those studied did not seem to differ obviously in terms of age at surgery, graft patency at one year, or the frequency of angina, nevertheless it is possible, particularly in the group in which either patient or physician refused restudy, that such patients might have had a better angiographic outcome. Even if this was so — and to take the extreme case, if none of these patients had any new disease — then the development of atherosclerosis would still remain a numerically important problem. It is also possible that the present results are biased favorably, since to be eligible for restudy a patient had to survive for 10 years after surgery. On the other hand, the strengths of this study are that the states of the graft and the native vessels were known both 1 and 10 years after surgery and that the sequential examinations were not performed because of symptoms.

Multivariate analysis demonstrated that plasma levels of LDL apoprotein B and HDL cholesterol were the principal factors that predicted the presence or absence of atherosclerosis. We must emphasize that this aspect of the study could not be prospective, since

Table 3. Total Lipid, Lipoprotein Lipid, and Plasma LDL Apoprotein B Levels 10 Years after Surgery.*

	Total Chol	Trg	LDL Chol	LDL apo B	HDL Chol
	milligrams per deciliter				
Group I	243±43	139±55	153±37	98±17	63±17
No. of patients	15	15	15	15	15
Group II	278±50	205±110	190±45	149±33	48±10
No. of patients	67	67	65	65	65
T value	−2.52	−2.25	−2.98	−5.89	4.37
P value	<0.01	<0.05	<0.005	<0.0001	<0.0001

*Plus–minus values are means ±S.D. Chol denotes cholesterol, trg triglyceride, LDL low-density-lipoprotein, apo B apoprotein B, and HDL high-density-lipoprotein.

Table 4. Lipoprotein and Apoprotein B Phenotypes 10 Years after Surgery.

PHENOTYPE	GROUP I (PATIENTS WITHOUT NEW LESIONS)	GROUP II (PATIENTS WITH NEW LESIONS)
No. of patients	*15*	*67*
	per cent	
Normal*	79	8
Normal + hyperapoB †	7	35
Hyperlipoproteinemia		
Type IIA	7	20
Type IIB	0	19
Hypertrg ‡	7	2
Hypertrg + HyperapoB §	0	17

*Indicates normal lipid and normal plasma LDL apoprotein levels.

†Indicates normal lipid and elevated plasma LDL apoprotein levels.

‡Indicates hypertriglyceridemia and normal levels of plasma LDL apoprotein B.

§Indicates hypertriglyceridemia and elevated levels of plasma LDL apoprotein B.

the potential role of these factors in the pathogenesis of arterial disease has only recently been appreciated. That is, interest in HDL cholesterol and risk of coronary-artery disease was rekindled only in the mid-1970s,[15] and the first evidence pointing to apoprotein B as an important risk factor for coronary disease did not appear until the end of the decade.[12,16] However, although the patients' original lipoprotein status was unfortunately evaluated incompletely, the demonstration that the univariate relations of plasma total cholesterol and triglyceride to the chance of disease were the same at the time of surgery and 10 years later suggests that there was no fundamental change over the study period.

The inverse relation between the risk of coronary disease and the level of HDL cholesterol is now well established, and this relation is confirmed again in the present study. That LDL apoprotein B levels are also related to the risk of coronary diseases is less widely known.[16] LDLs are complex particles containing most of the serum cholesterol. But because the content of cholesterol per LDL particle may vary widely, LDL cholesterol is often an inaccurate index of the amount of plasma LDL.[17] By contrast the content of apoprotein B per particle appears to be constant and thus an accurate index of the number of LDL particles per milliliter of plasma. Thus, the measurement of plasma levels of LDL apoprotein B may turn out to be an important and economical way to distinguish the clinically normal from the abnormal. Of the 67 patients in whom new disease developed, 90 per cent had elevated plasma levels of LDL apoprotein B; of these, less than half had an elevated level of LDL cholesterol, whereas the majority had hyperapobetalipoproteinemia — that is, an elevated LDL apoprotein B level with a normal level of LDL cholesterol.

Finally, although we have emphasized the factors that should limit generalization from the present data to the very large number of patients who have undergone saphenous-vein aortocoronary bypass surgery, the long-term patency rates of saphenous-vein bypass grafts documented in this study are undoubtedly disappointing. Nonetheless, the observation that atherosclerosis occurs in grafts or progresses in the native coronary arteries of patients who have already demonstrated susceptibility to this disease is hardly surprising. The relation between plasma LDL apoprotein B and HDL cholesterol levels and the risk of disease in this study is striking and may be a clue to its prevention.

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